Long-term in vivo monitoring of mouse and human hematopoietic stem cell engraftment with a human positron emission tomography reporter gene.

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Public Summary:
Therapies utilizing transplanted cells to treat a patient's disease are being developed for previously untreatable conditions. These transplanted cells are complex and living unlike conventional medicines and require close monitoring for efficacy or adverse events. Physicians and researchers need tools to be able to broadly track these cells after transplant without invasive measures (biopsies). Positron Emission Tomography (PET) is a clinical whole-body imaging technology which can track the location of radioactive probes. Probes can be developed to monitor a wide range of events including metabolism, and cell specific detection. One method to detect specific cell populations is the use of PET reporter genes. These genes are able to genetically mark cells prior to transplantation allowing for reporter detection of transplanted cells when imaged with a specific probe through whole body PET imaging. Past reporter genes used viral proteins which caused a rejection in cells expressing this gene. To overcome this issue we developed a human based PET reporter gene (hdCK3mut) which should eliminate the previously seen rejection of cells. hdCK3mut is human deoxycytidine kinase with three amino acid substitutions in the protein. These substitutions allow cells that carry hdCK3mut to be detected with the PET probe [18F]-L-FMAU. We found that normal cells would not accumulate [18F]-L-FMAU and that signal is only detected in cells with hdCK3mut. We tested hdCK3mut reporter imaging in mice that were given reporter labeled blood stem cells. In the cells which contained hdCK3mut we could visualize these cells within the bone marrow, spleen and thymus by [18F]-L-FMAU PET. Animals were scanned multiple times and cells could be detected throughout the animals' life span. We found that hdCK3mut labeled cells were identical to non-labeled cells in all additional assays measured. These studies demonstrated that hdCK3mut is safe and can be used as a long-term monitoring tool for stem cell therapies. We anticipate that hdCK3mut will be a valuable tool for physicians and researchers in a wide range of cell based therapies.

Scientific Abstract:
Positron emission tomography (PET) reporter genes allow noninvasive whole-body imaging of transplanted cells by detection with radiolabeled probes. We used a human deoxycytidine kinase containing three amino acid substitutions within the active site (hdCK3mut) as a reporter gene in combination with the PET probe [(18)F]-L-FMAU (1-(2-deoxy-2-(18)fluoro-beta-L-arabinofuranosyl)-5-methyluracil) to monitor models of mouse and human hematopoietic stem cell (HSC) transplantation. These mutations in hdCK3mut expanded the substrate capacity allowing for reporter-specific detection with a thymidine analog probe. Measurements of long-term engrafted cells (up to 32 wk) demonstrated that hdCK3mut expression is maintained in vivo with no counter selection against reporter-labeled cells. Reporter cells retained equivalent engraftment and differentiation capacity being detected in all major hematopoietic lineages and tissues. This reporter gene and probe should be applicable to noninvasively monitor therapeutic cell transplants in multiple tissues.

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